The gene expression profiles of induced pluripotent stem cells from individuals with childhood cerebral adrenoleukodystrophy are consistent with proposed mechanisms of pathogenesis.

Journal: Stem Cell Res Ther

Publication Year: 2012

Authors: Xiao-Ming Wang, Wing Yan Yik, Peilin Zhang, Wange Lu, Patricia K Dranchak, Darryl Shibata, Steven J Steinberg, Joseph G Hacia

PubMed link: 23036268

Funding Grants: Regulation of human neural progenitor cell proliferation by Ryk-mediated Wnt signaling, Defining the molecular mechanisms of somatic cell reprogramming, CIRM Stem Cell Biology Training Program, CIRM Stem Cell Biology Training Grant

Public Summary:
X-linked adrenoleukodystrophy (X-ALD) is a complex disorder that affects the nervous, adrenocortical, and male reproductive systems. Although ABCD1 mutations are known to provide the genetic basis for X-ALD, its pathogenesis is not fully elucidated. Primary skin fibroblasts from two male patients with the childhood cerebral form of disease (CCALD) caused by ABCD1 mutations and three healthy donors were transduced with retroviral vectors expressing the OCT4, SOX2, KLF4, and c-MYC factors. Induced pluripotent stem cells (iPSCs) were subject to global gene expression, DNA methylation, DNA copy number variation, and genotyping analysis and tested for pluripotency through in vitro differentiation and teratoma formation. Unlike fibroblasts, CCALD patient iPSCs show differentially expressed genes relevant to both peroxisome abundance and neuroinflammation. The highlighted genes provide new leads for pathogenic mechanisms that can be explored in animal models and human tissue specimens. We suggest that these iPSC resources will have applications that include assisting efforts to identify genetic and environmental modifiers and screening for therapeutic interventions tailored towards affected cell populations and patient genotypes.

Scientific Abstract:
ABSTRACT: INTRODUCTION: X-linked adrenoleukodystrophy (X-ALD) is a complex disorder with variable expressivity that affects the nervous, adrenocortical, and male reproductive systems. Although ABCD1 mutations are known to provide the genetic basis for X-ALD, its pathogenesis is not fully elucidated. While elevated very long chain fatty acid (VLCFA) levels in blood and reduced VLCFA catabolic activity in cultured fibroblasts are biomarkers used to identify ABCD1 mutation carriers, the roles peroxisomal lipid metabolism play in disease etiology are unknown. METHODS: Primary skin fibroblasts from two male patients with the childhood cerebral form of disease (CCALD) caused by ABCD1 frameshift or missense mutations and three healthy donors were transduced with retroviral vectors expressing the OCT4, SOX2, KLF4, and c-MYC factors. Candidate induced pluripotent stem cells (iPSCs) were subject to global gene expression, DNA methylation, DNA copy number variation, and genotyping analysis and tested for pluripotency through in vitro differentiation and teratoma formation. Saturated VLCFA (sVLCFA) and plasmalogen levels in primary fibroblasts and iPSCs from healthy donors as well as CCALD patients were determined through mass spectroscopy. RESULTS: Skin fibroblasts from CCALD patients and healthy donors were reprogrammed into validated iPSCs. Unlike fibroblasts, CCALD patient iPSCs show differentially expressed genes (DEGs) relevant to both peroxisome abundance and neuroinflammation. Also, in contrast to fibroblasts, iPSCs from patients showed no significant difference in sVLCFA levels relative to those from controls. In all cell types, the plasmalogen levels tested did not correlate with ABCD1 mutation status. CONCLUSION: Normal ABCD1 gene function is not required for reprogramming skin fibroblasts into iPSCs or maintaining pluripotency. Relative to DEGs found in fibroblasts, DEGS uncovered in comparisons of CCALD patient and control iPSCs are more consistent with major hypotheses regarding disease pathogenesis. These DEGS were independent of differences in sVLCFA levels, which did not vary according to ABCD1 mutation status. The highlighted genes provide new leads for pathogenic mechanisms that can be explored in animal models and human tissue specimens. We suggest that these iPSC resources will have applications that include assisting efforts to identify genetic and environmental modifiers and screening for therapeutic interventions tailored towards affected cell populations and patient genotypes.